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PATENT SPECIFICATION

NO DRAWINGS

Inventors: JOSEF KRAMER, HERBERT HALPAAP and KARLO-OTTO FRIESBERG

1,154,119

1,154,119

Date of Application and filing Complete Specification: 20 May, 1968.

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Int. Cl.: —C 07 d 7/32

COMPLETE SPECIFICATION

3-Alkyl-Flavanones

ERRATUM

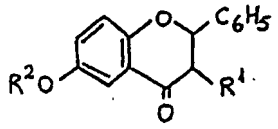
SPECIFICATION NO. 1,154,119

Page 1, for Index at Acceptance C2C only read:-

(3A8A4, 3A8B2, 3A8C1, 3A8D2, 3A8G1, 3A12A4B, 3A12B1, 3A12C5, 3C7, P3B13, P3B15A, P3B16, P3B19E, P7, 213, 22Y, 220, 226, 227, 25Y, 253, 29Y, 290, 30Y, 32Y, 323, 351, 352, 355, 36Y, 364, 365, 650, 662, 672, 760, 79Y, 790, 179 - 199 - 278, LM)

THE PATENT OFFICE,
30th December 1969

D 120681/17



(1)

wherein R^1 is an alkyl radical containing up to 6 carbon atoms, R^2 is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms or the radical $Z-(CH_2)_n-$, Z is a dialkylamino radical containing 2—6 carbon atoms or a pyrrolidino, piperidino or morpholino radical and n is 2 or 3; and the esters, acid addition salts, ester salts and quaternary ammonium compounds thereof.

We have found that the new 3 - alkyl - flavanones (I) according to the present invention possess valuable pharmacological properties and can, therefore, be used as pharmaceuticals. In particular, they show a choles-

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... mg./kg., there are obtained the percentage lowerings of the cholesterol level in rats (for the method used see Counsell et al., J. med. pharm. Chem., 5, 720, 1224(1962) which are indicated in the following:

3 - methyl - 6 - hydroxyflavanone - 6 - sulphate, sodium salt (A)	86%
3 - methyl - 6 - hydroxyflavanone	42%
3 - n - propyl - 6 - hydroxy - flavanone	37%
3 - n - propyl - 6 - hydroxy - flavanone - 6 - nicotinate, cis - trans mixture (B):	36%

The new compounds according to the present invention also show a good compatibility. Their toxicities are extraordinarly low For example, the LD_{50} of the abovementioned compound (A) is more than 3.2 g./kg. and that of compound (B) is more than 6.4 g./kg. (determined orally in rats).

Furthermore, the new compounds (I) can

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Int. Cl.: —C 07 d 7/32

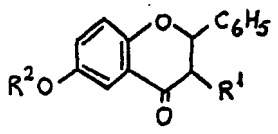
COMPLETE SPECIFICATION

3-Alkyl-Flavanones

We, E. MERCK AKTIENGESELLSCHAFT, of 250 Frankfurter Strasse, 61 Darmstadt, Germany, a Joint-Stock Company organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described, in and by the following statement:—

The present invention is concerned with new 3 - alkylflavanones and with the preparation thereof.

The new 3 - alkyl - flavanones according to the present invention are compounds of the general formula:—



(1)

wherein R^1 is an alkyl radical containing up to 6 carbon atoms, R^2 is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms or the radical $Z—(CH_2)_n—$, Z is a dialkylamino radical containing 2—6 carbon atoms or a pyrrolidino, piperidino or morpholino radical and n is 2 or 3; and the esters, acid addition salts, ester salts and quaternary ammonium compounds thereof.

We have found that the new 3 - alkyl - flavanones (I) according to the present invention possess valuable pharmacological properties and can, therefore, be used as pharmaceuticals. In particular, they show a cholesterol level-lowering action without, however, causing a non-physiological enrichment of desmosterol or of 7 - dehydrocholesterol in the sterines of the serum or of the liver, as is the case with known cholesterol level-lowering agents, such as 22,25 - diaza - cholesterol, triparanol and dehydroepiandro - sterone - 3 - diethylaminoethyl ether. Furthermore, the new flavanone derivatives according to the present invention show an oestrogenic and anti-fertility activity.

Thus, for example, in the case of the oral administration of the following new compounds according to the present invention in amounts of 50 mg./kg., there are obtained the percentage lowerings of the cholesterol level in rats (for the method used see Counsell et al., J. med. pharm. Chem., 5, 720, 1224(1962) which are indicated in the following:

3 - methyl - 6 - hydroxyflavanone - 6 - sulphate, sodium salt (A)	86%
3 - methyl - 6 - hydroxyflavanone	42%
3 - n - propyl - 6 - hydroxy - flavanone	37%
3 - n - propyl - 6 - hydroxy - flavanone - 6 - nicotinate, cis - trans mixture (B):	36%

The new compounds according to the present invention also show a good compatibility. Their toxicities are extraordinarly low For example, the LD_{50} of the abovementioned compound (A) is more than 3.2 g./kg. and that of compound (B) is more than 6.4 g./kg. (determined orally in rats).

Furthermore, the new compounds (I) can

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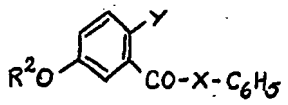
also be used as intermediates for the preparation of other pharmaceuticals.

The new compounds according to the present invention can be prepared, for example, by treating a ketone of the general formula:—



(II)

wherein X is $-CR^1=CH-$ or $-CHR^1-CHY-$, Y is a chlorine bromine or iodine atom of a hydroxyl group, with the proviso that when two Y's are present, at least one of them is a hydroxyl group, and R^1 and R^2 have the same meanings as above and wherein hydroxyl groups can also be present in a functionally changed form, which ketone can also be produced in situ, with a cyclising agent and a functionally changed hydroxyl group present in the product obtained can be liberated in known manner by hydrolysis or hydrogenolysis and/or a free hydroxyl group is esterified or alkylated, possibly in a multi-step process, and/or a compound (I) is, if desired, converted into a physiologically compatible acid-addition salt, ester salt or quaternary ammonium compound by treatment with an acid, base or alkylation agent, respectively.

As examples of alkyl radicals R^1 and R^2, there may be mentioned methyl, ethyl, propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl, n-amyl, isoamyl, n-hexyl and isohexyl radicals.

As examples of $Z-(CH_2)_n-$ groups in the radical R^2, there may, in particular, be mentioned 2 - dimethylaminoethyl, 2 - diethylaminoethyl, 3 - dimethylaminopropyl, 3 - diethylamino - propyl, 2 - pyrrolidino - ethyl, 2 - piperidino - ethyl, 2 - morpholino - ethyl, 3 - pyrrolidino - propyl, 3 - piperidino-propyl and 3 - morpholino - propyl radicals.

As esters of those compounds of general formula (I) in which R^2 is a hydrogen atom, there may, in particular, be mentioned the lower acylates in which the acyl radical contains up to 6 carbon atoms. More particularly, examples of such esters include the formates, acetates, propionates, butyrates, isobutylates, valerianates, isovalerianates, trimethyl - acetates, capronates and isocapronates, as well as, for example, the nitoctinates, isonicotinates, diethylaminoacetates and the acid addition salts thereof, preferably the hydrochlorides. The sulphuric acid and phosphoric acid esters and the physiologically compatible metal salts, especially the alkali metal salts, such as the sodium salts, and the ammonium salts thereof are particularly important because they are water-soluble derivatives of the compounds (I) and thus are compounds which, therapeutically, are particularly easy to administer.

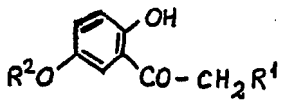
The expression "ester salts" is, according to the present invention, to be understood to mean the acid addition salts of basically substituted esters and the metal and ammonium salts of acid esters.

As compounds of general formula (II), the chalcones ($X=-CR^1=CH-$) are particularly preferred.

The compounds of general formula (II) can, in particular, be cyclised by the action of basic or acid catalysts to give the flavanones of general formula (I). As catalysts, there are preferably used alkalis, such as sodium or potassium hydroxide, sodamide or sodium hydride; basically-reacting salts, such as sodium or potassium acetate or sodium or potassium carbonate; buffer solutions, for example, those of citric acid and disodium phosphate or of sodium or potassium hydrogen phosphate and borax or of boric acid, sodium hydroxide and potassium chloride; organic bases, such as piperidine, pyridine, tetramethyl-guanidine or benzyl-trimethyl-ammonium hydroxide; mineral acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or polyphosphoric acids; or organic sulphonic acids, such as toluene-sulphonic acid or camphor-sulphonic acid.

The cyclising can be carried out in the presence of an inert solvent, such as methanol, ethanol, dioxan, tetra-hydrofuran, ethyl acetate, 1,2,3,4 - tetrahydronaphthalene, benzene or toluene, or possibly in a mixture of these solvents with one another or with water. It is, however, also possible to use an excess of the cyclising agent as solvent. The cyclising can be carried out at the ambient temperature but can be accelerated by warming, possibly up to the boiling point of the solvent used. The reaction time amounts to a few minutes to a few days.

The chalcones are preferably obtained by the condensation of a 5 - substituted 2 - hydroxyphenyl - alkyl ketone of the general formula:—



(III)

wherein R^1 and R^2 have the same meanings as above and hydroxyl groups can also be present in a functionally changed form, with benzaldehyde or also from a p-substituted phenol and a cinnamic acid derivative in the presence of aluminium chloride.

It is not necessary to isolate the chalcone used as starting material; on the contrary,

the reaction mixture obtained from the ketone (III) and benzaldehyde can be treated directly with the cyclising agent.

A particularly preferred method of carrying out the preparation of the new compounds according to the present invention consists in treating a mixture of a ketone (III) and benzaldehyde with a base, such as sodium hydroxide, potassium hydroxide or piperidine. The base thereby serves not only as a condensation agent for the formation of the chalcone but also as a cyclising agent. The reaction can be carried out with or without the addition of a solvent. Preferred solvents are the lower alcohols, such as methanol, ethanol, isopropanol or tert.-butanol. The reaction is expediently completed by heating the reaction mixture for several hours.

Typical examples of ketones of general formula (III) includes 2,5 - dihydroxyphenyl-ethyl ketone (-propiophenone), -propyl ketone (-butyrophenone), -n-butyl ketone, -isobutyl ketone, -n-amyl ketone, -isoamyl ketone, -n-hexyl ketone, -isohexyl ketone, -n-heptyl ketone and -isoheptyl ketone; 2 - hydroxy - 5 - methoxyphenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone; 2 - hydroxy - 5 - ethoxy - phenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone; 2 - hydroxy - 5 - n - propoxyphenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone; 2 - hydroxy - 5 - isopropoxyphenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone; 2 - hydroxy - 5 - isobutoxyphenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone; and 2 - hydroxy - 5 - isoamyloxyphenyl - ethyl ketone, -propyl ketone, -n-butyl ketone and -isobutyl ketone.

In the case of the above-mentioned reactions of the compounds of the general formulae (II) and (III), it is possible for phenolic hydroxyl groups to be present in a functionally changed form. Under the conditions of the condensation, such functionally changed hydroxyl groups can be liberated. Thus, compounds, in which the hydroxyl groups are present protected as tetrahydropyranyl ethers, can be cyclised in acidic or alkaline media; in the case of an alkaline cyclisation, the hydroxyl group can be liberated by a subsequent brief boiling with an acid. Compounds containing ester groups as the protected hydroxyl groups can also be condensed in acidic or alkaline media, whereby the ester group can be saponified.

Furthermore, ether groups, such as benzyl ether or methyl ether groups, can be used as protective groups. The splitting of such ethers can take place, for example, when, as cyclising agent, there is used hydrobromic acid under such conditions under which it is known that splitting of phenol ethers takes place.

Insofar as functionally changed hydroxyl groups are still present in the cyclisation products obtained, then they are liberated in known manner by treatment with hydrolysing or hydrogenolysing agents. Thus, for example, it is possible to hydrolyse an esterified hydroxyl group by treatment with basic or acidic agents. As bases, there are preferably used aqueous, aqueous alcoholic or alcoholic sodium or potassium hydroxide and, as acids, preferably hydrochloric acid or sulphuric acid. Benzyl ethers can be split by hydrogenolysis in the presence of noble metal catalysts, such as palladium charcoal, the basic hydroxyl group thereby being liberated.

Furthermore, it is possible, if desired, to esterify or to alkylate free hydroxyl groups.

An esterification of hydroxyl groups can be carried out, for example, by heating with an anhydride or halide of a carboxylic acid, preferably one containing up to 6 carbon atoms. Typical examples of such acids include acetic, propionic, butyric, isobutyric, valeric, isovaleric, capronic, nicotinic and isonicotinic acids. The esterification is preferably carried out in the presence of a base, such as pyridine, or of an alkali metal salt of the corresponding acid or also of a small amount of a mineral acid, such as sulphuric acid or hydrochloric acid.

For the preparation of the sulphuric acid and phosphoric acid esters of compounds of general formula (I) (R^2 is a hydrogen atom), these are reacted with sulphuric acid, phosphoric acid or a derivative of these acids which is suitable for esterification purposes, using methods which are known from the literature.

It is also possible to carry out the reaction with a sulphuric acid or phosphoric acid derivative in which one of two hydroxyl groups are blocked and subsequently to remove, by hydrolysis or hydrogenolysis, the protective groups present in the esters obtained. Finally, the sulphuric acid or phosphoric acid esters obtained can be converted with bases into their physiologically compatible metal and ammonium salts.

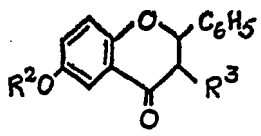
An alkylation can be carried out, for example, by reaction with alkyl halides, sulphates or lower alkyl esters, the alkyl radicals of which contain up to 6 carbon atoms. For the preparation of the dialkylaminoalkyl ethers, there are used dialkylaminoalkyl halides, sulphates or lower dialkylaminoalkyl esters, the dialkylaminoalkyl groups of which contain 4—8 carbon atoms. As a rule, the reaction is carried out in the presence of alkalis, such as sodium or potassium hydroxide or carbonate, whereby one of the usual solvents can also be present. Consequently, the starting compounds can be reacted with methyl iodide, dimethyl sulphate, ethyl, propyl, isopropyl, butyl, isobutyl, amyl and isoamyl halides, 2-dimethyl-aminoethyl, 2-diethyl-aminoethyl, 2-(methyl-

ethylamino)-ethyl, 2-pyrrolidino-ethyl, 2-morpholino-ethyl, 3-dimethylamino-propyl, 3-diethylaminopropyl, 3-pyrrolidino-propyl, 3-piperidino-propyl or 3-morpholino-propyl halides or also with the corresponding alcohols. As halides, there can be used the chlorides, bromides and iodides. The etherification can be carried out, for example, by means of a Williamson synthesis, starting from the corresponding alkali metal phenolates. However, it is also possible to react the free phenols with the corresponding alcohols or substituted amino-alcohols in the presence of acidic catalysts, such as sulphuric acid, phosphoric acid or p-toluene-sulphonic acid.

Furthermore, it is possible to convert basic compounds of general formula (I) into their physiologically compatible acid addition salts by treatment with acids. For this reaction, there can be used organic and inorganic acids, such as aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or poly-basic carboxylic and sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethyl-acetic acid, oxalic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, and malic acid; aminocarboxylic acids; sulphamic acids; benzoic acid, salicyclic acid, phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, isonicotinic acid, methane-sulphonic acid, naphthalene-mono- and di-sulphonic acids, sulphuric acid and nitric acid; hydrohalic acids, such as hydrochloric acid or hydrobromic acid, or phosphoric acids, such as orthophosphoric acid.

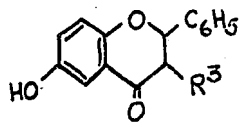
A conversion of the basic flavanones of general formula (I) into their physiologically compatible quaternary ammonium derivatives can be carried out by treatment with alkylation agents, such as methyl iodide, dimethyl sulphate, ethyl bromide or ethyl iodide.

Preferred compounds according to the present invention are those of the following general formulae:



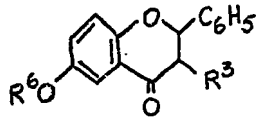
(IV)

wherein R^3 is a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-amyl, isoamyl, n-hexyl or isohexyl radical and R^2 has the same meaning as above;



(V)

wherein R^3 has the same meaning as above; and



(VI)

wherein R^6 is hydrogen atom or an R^7—$(CH_2)_n$— group and R^7 is a dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino radical.

The new compounds according to the present invention can be used in admixture with conventional pharmaceutical carriers used in human and veterinary medicine. As carrier materials there can be used those organic or inorganic materials which are suitable for parenteral, enteral or topical administration and which do not react with the new compounds, for example, water, vegetable oils, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, petroleum jelly and cholesterol. For parenteral administration, there are preferably used solutions, especially oily or aqueous solutions, as well as suspensions or emulsions. For enteral adminstration, there can also be used tablets or dragees, for topical application, salves or creams, which can be sterilised or mixed with adjuvants, such as preservation, stabilisation or wetting agents or salts for influencing the osmotic pressure or with buffer substances.

The new alkyl-flavanones according to the present invention are preferably administered at a dosage rate of 1—500 mg. per dosage unit.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1

a) 1 g. benzaldehyde and 1.6 g. 2,5 - di - hydroxy - propiophenone are boiled for 15 hours in 8 ml. dry piperidine and 14 ml.

absolute ethanol. The reaction mixture is then stirred into ice water, followed by acidification with hydrochloric acid and extraction with chloroform. The organic phase is washed with water, dried over anhydrous sodium sulphate and then evaporated to dryness. After recrystallising the residue from benzene, there is obtained 3 - methyl - 6 - hydroxy - flavanone, which has a melting point of 174—176°C.

The following compounds are obtained in an analogous manner from the corresponding 2,5 - dihydroxy - phenyl - alkyl ketones:

3 - ethyl - 6 - hydroxy - flavanone; m.p. 147—149°C.;
3 - n - propyl - 6 - hydroxy - flavanone; m.p. 145—146°C.;
3 - isopropyl - 6 - hydroxy - flavanone;
3 - n - butyl - 6 - hydroxy - flavanone;
3 - isobutyl - 6 - hydroxy - flavanone;
3 - n - amyl - 6 - hydroxy - flavanone;
3 - isoamyl - 6 - hydroxy - flavanone;
3 - n - hexyl - 6 - hydroxy - flavanone;
3 - isohexyl - 6 - hydroxy - flavanone;

b) A solution of 1 g. 3 - ethyl - 6 - hydroxy - flavanone in 20 ml. acetone is mixed with an etheral solution of 5 g. diethylaminoethyl chloride and 1 g. anhydrous potassium carbonate, the reaction mixture boiled for 20 hours, then stirred into water and extracted with chloroform. The extract is washed with water, dried over anhydrous sodium sulphate and evaporated to dryness, the residue dissolved in ethanol and the solution mixed with an ethanolic solution of oxalic acid. After standing for some time, the oxalate of 3 - ethyl - 6 - (2 - diethylaminoethoxy) - flavanone crystallises out; it has a melting point of 134—135°C.

In an analogous manner, there is obtained the hydrochloride of 3 - methyl - 6 - (2 - diethylaminoethoxy) - flavanone, which has a melting point of 168—170°C.

c) A solution of 1 g. 3 - methyl - 6 - hydroxy - flavanone in 6 ml. pyridine is mixed at 90°C. with 1.1 g. amidosulphonic acid and the reaction mixture stirred for 3 hours at 90°C. The reaction mixture is cooled, washed with 30 ml. ether, the pyridine phase mixed with 17 ml. 12% sodium hydroxide solution and 12 ml. pyridine, separated, again washed with ether and then evaporated. There is obtained the sodium salt of 3 - methyl - 6 - hydroxyflavanone - 6 - sulphuric acid ester which, after recrystallisation from ethanol, has a melting point of 178—180°C.

d) 1 g. 3 - n - propyl - 6 - hydroxy - flavanone is heated for 30 minutes on a steambath in a mixture of 5 ml. anhydrous pyridine and 5 ml. nicotinic acid chloride. The reaction mixture is poured into water and filtered with suction. The material obtained is dried, dissolved in a little ethanol and, by the addition of ethereal hydrochloric acid, the hydrochloride of the nicotinic acid ester of 3 - n - propyl - 6 - hydroxyflavanone precipitates out. It has a melting point of 168—170°C. The free base is obtained from the hydrochloride by the action of sodium hydroxide solution and, by fractional crystallisation from methanol, is separated into cis- and trans - 3 - n - propyl - 6 - hydroxyflavanone - 6 - nicotinate, which melt at 131—133°C. and 90—92°C., respectively.

e) 1 g . 3 - methyl - 6 - hydroxyflavanone is heated for 5 hours at 50°C. in 5 ml. pyridine and 5 ml. acetic anhydride. After cooling the reaction mixture, water and chloroform are added thereto, separated and the chloroform layer is washed several times with water and the chloroform then distilled off. There is obtained 3 - methyl - 6 - acetoxy - flavanone which, after recrystallisation from methanol, has a melting point of 127—129°C.

f) 7.5 g. 3 - methyl - 6 - hydroxyflavanone dissolved in 100 ml. pyridine are added dropwise with stirring at a temperature of 5°C. and in the course of 15 minutes to a solution of 20 ml. phosphorous oxychloride in 210 ml. anhydrous pyridine. The reaction mixture is left to stand overnight at the ambient temperature, the reaction mixture then poured on to a mixture of ice and concentrated hydrochloric acid and thereafter heated on a steambath for 90 minutes. After cooling, the reaction mixture is extracted with ethyl acetate, the extracts are washed with dilute hydrochloric acid, dried over anhydrous sodium sulphate, filtered, the solvent distilled off to give 3 - methyl - 6 - hydroxyflavanone - 6 - orthophosphate.

Example 2

a) 1 g. α - benzylidine - 2 - hydroxy - 5 - (2 - diethylamino - ethoxy) - propiophenone (obtained by the condensation of 2 - hydroxy-5 - (diethylaminoethoxy) - propiophenone with benzaldehyde in aqueous-methanolic sodium hydroxide solution at ambient temperature) is heated for 2 hours at 130°C. in a bomb tube in 50 ml. ethanol in the presence of 1 g. p - toluene - sulphonic acid. The reaction mixture is cooled, dilute sodium hydroxide solution and chloroform added thereto, separated and the chloroform layer dried over anhydrous sodium sulphate and then evaporated to dryness. The residue is dissolved in ethanol and mixed with ethereal hydrochloric acid. There is obtained 3 - methyl - 6 - (2 - diethylaminoethoxy) - flavanone hydrochloride, which has a melting point of 168—170°C.

b) 0.5 g. of the hydrochloride obtained in (a) above is shaken with 2 ml. dilute sodium hydroxide solution and 10 ml. ether, the layers are separated, the ethereal phase is dried over anhydrous magnesium sulphate

and mixed with an excess of methyl iodide. After standing for 2 hours, the precipitated 3 - methyl - 6 - (2 - diethylaminoethoxy) - flavanone methiodide is filtered off.

EXAMPLE 3

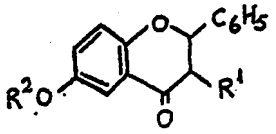
1 g. 2 - hydroxy - 5 - benzyloxy - propiophenone and 0.5 g. benzaldehyde are dissolved in 10 ml. ethanol, mixed with 5 g. 50% potassium hydroxide solution and shaken for 5 minutes. The reaction mixture is mixed with water, filtered with suction and carefully washed with water. There is obtained 3 - methyl - 6 - benzyloxy - flavanone which, without purification, is hydrogenolysed in 40 ml. ethyl acetate saturated with hydrogen chloride in the presence of 5% palladium charcoal at a temperature of 35°C. until the calculated amount of hydrogen has been taken up. The catalyst is then filtered off, the solvent is removed and the 3 - methyl - 6 - hydroxyflavanone obtained is recrystallised from benzene. It has a melting point of 174—176°C.

EXAMPLE 4

2 g. 2 - hydroxy - 5 - (tetrahydropyranyl-2 - oxy) - propiophenone are reacted with benzaldehyde in a manner analogous to that described in Example 3 and the crude 3 - methyl - 6 - (tetrahydropyranyl - 2 - oxy) - flavanone obtained boiled for 2 hours with 5% aqueous-ethanolic hydrochloric acid. The reaction mixture is stirred into water and then worked up in the manner described in Example 1 a). There is obtained 3 - methyl-6 - hydroxyflavanone, which has a melting point of 174—176°C.

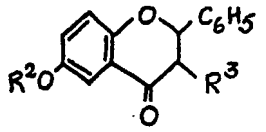
WHAT WE CLAIM IS:—

1. 3 - Alkyl - flavanones of the general formula:—



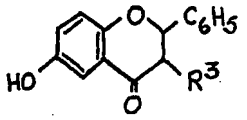
wherein R^1 is an alkyl radical containing up to 6 carbon atoms, R^2 is a hydrogen atom or an alkyl radical containing up to 6 carbon atoms or a $Z—(CH_2)_n—$ group, Z is a dialkylamino radical containing 2—6 carbon atoms or a pyrrolidino, piperidino or morpholino radical and n is 2 or 3, and the esters, acid addition salts, ester salts and quaternary ammonium derivatives thereof.

2. 3 - Alkyl - flavanones of the general formula:—



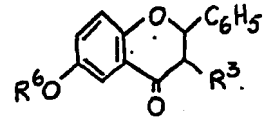
wherein R^2 has the same meaning as in Claim 1 and R^3 is a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-amyl, isoamyl, n-hexyl or isohexyl radical.

3. 3 - Alkyl - flavanones of the general formula:—



wherein R^3 has the same meaning as in Claim 2.

4. 3 - Alkyl - flavanones of the general formula:—



wherein R^6 is a hydrogen atom or an $R^7—(CH_2)_n—$ group and R^7 is a dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino radical.

5. 3 - Methyl - 6 - hydroxyflavanone.
6. 3 - Ethyl - 6 - hydroxyflavanone.
7. 3 - n - propyl - 6 - hydroxyflavanone.
8. 3 - Isopropyl - 6 - hydroxyflavanone.
9. 3 - n - Butyl - 6 - hydroxyflavanone.
10. 3 - Isobutyl - 6 - hydroxyflavanone.
11. 3 - n - Amyl - 6 - hydroxyflavanone.
12. 3 - Isoamyl - 6 - hydroxyflavanone.
13. 3 - n - Hexyl - 6 - hydroxyflavanone.
14. 3 - Isohexyl - 6 - hydroxyflavanone.
15. 3 - Ethyl - 6 - (2 - diethylaminoethoxy) - flavanone oxalate.
16. 3 - Methyl - 6 - (2 - diethylaminoethoxy) - flavanone hydrochloride.
17. 3 - Methyl - 6 - hydroxyflavanone - 6 - sulphuric acid ester.
18. 3 - n - Propyl - 6 - hydroxyflavanone nicotinate hydrochloride.

19. cis - 3 - n - Propyl - 6 - hydroxyflavanone - 6 - nicotinate.

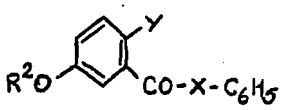
20. trans - 3 - n - Propyl - 6 - hydroxyflavanone - 6 - nicotinate.

21. 3 - Methyl - 6 - acetoxy - flavanone.

22. 3 - Methyl - 6 - hydroxyflavanone - 6 - orthophosphate.

23. 3 - Methyl - 6 - (2 - diethylaminoethoxy) - flavanone methiodide.

24. A process for the preparation of compounds according to Claim 1, wherein a ketone of the general formula:—

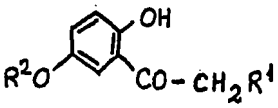


in which X is a $-CR^1=CH-$ or $-CHR^1-CHY-$ group, Y is a chlorine, bromine or iodine atom or a hydroxy group with the proviso that when two Y's are present, at least one of them is a hydroxy group, and R^1 and R^2 have the same meanings as in Claim 1 and wherein hydroxyl groups can also be present in functionally changed form, is treated with a cyclisation agent, whereafter, groups present in the product obtained are converted into free hydroxyl groups by hydrolysis or hydrogenolysis and/or free hydroxyl groups present in the product obtained are esterified or alkylated by treatment with esterification or alkylation agents and/or the product obtained is converted into a physiologically compatible acid-addition salt, ester salt or quaternary ammonium derivative by treatment with an acid, base or alkylation agent.

25. Process according to Claim 24, wherein the cyclisation is carried out with the use of an acidic or basic catalyst.

26. Process according to Claim 24 or 25, wherein the cyclisation is carried out in an inert solvent or in an excess of cyclising agent.

27. Process according to any of Claims 24—26, wherein the ketone used as starting material is obtained by the condensation of a 5-substituted 2-hydroxyphenyl-alkyl ketone of the general formula:—



wherein R^1 and R^2 have the same meanings as in Claim 1 and the hydroxyl groups present can be in a functionally changed form, with benzaldehyde or by the reaction of a p-substituted phenol with a cinnamic acid derivative in the presence of aluminium chloride, the product obtained being isolated before further reaction or being used without isolation for the cyclisation reaction.

28. Process for the preparation of compounds of the general formula given in Claim 1, wherein a ketone of the general formula given in Claim 27 is reacted with benzaldehyde in the presence of a base.

29. Process for the preparation of compounds according to Claim 1, substantially as hereinbefore described and exemplified.

30. Compounds according to Claim 1, whenever prepared by the process according to any one of Claims 24—29.

31. Pharmaceutical compositions, containing at least one compound according to Claim 1 in admixture with a pharmaceutical carrier.

32. Pharmaceutical compositions according to Claim 31, whenever in a dosage unit form containing from 1 to 500 mg. of at least one compound according to Claim 1.

33. Process for obtaining a reduction in the cholesterol level and/or of obtaining oestrogenic and/or anti-fertility effects in mammals (excluding human beings), wherein there is administered an effective dose of a compound according to Claim 1.

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